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BY FACSIMILE

Dear Sirs

Opposition to European Patent No. EP-B-0839039
Proprietor: SmithKline Beecham plc
Our Ref: IMA/6174775

In connection with the summons to oral proceedings, I file the following observations.

A. Objections to new main claim request:

Claim 2 is redundant in view of the recital of paroxetine in claim 1, so the amended claims are not concise as required by Art 84. Moreover, the amended claims lack clarity (Art 84) by virtue of the implication that claim 1 is somehow broader than claim 2 but without it being clear how; and by virtue of the mention of "the SSRI" in claim 2, which no longer has an antecedent.

Claim 4: This appears to be a controlled release formulation, and not a controlled and delayed formulation as required by claim 1. The claims therefore lack clarity (Art 84) by virtue of the appendancy of claim 4 to claim 1.

Claim 5: This is specified as being a controlled release formulation, not a controlled and delayed release formulation, and therefore subject to the same objection as for claim 4.

That these were intended to be controlled release (only) is further emphasized by the disclosure in para 0018, on which this is presumably based, and which is followed in para 0018 by a reference to **US patent 5422123** (copy filed herewith), which discloses controlled release formulations, but makes no mention of delayed release.

This confusion of "controlled release" and "delayed release" is further commented on below.

B. Novelty:

In my notice of opposition I argued that there was still a case to answer in respect of **D24** (D1 as previously numbered). Proprietor's response was to the effect that the Eudragit polymers referred to in that disclosure are delayed release agents and not controlled release agents. Proprietor also seemed to be saying that they are only delayed release agents

when used to provide an enteric coating. Proprietor's argument is that in **D24** the Eudragit is not acting as a delayed release agent since the formulation is intended to be chewed, and must therefore be an immediate release formulation.

The problem with this is that the manner in which the terms "controlled release" and "delayed release" are defined in the opposed patent does not allow a clear distinction to be made over **D24**. Thus, in **D24** it is stated at the outset that the problem to be overcome is the unpleasant taste of drugs that come into direct contact with the mouth; and even polymer-coated drugs can be released if the polymer breaks down in the mouth, "particularly when chewed" (the inference being that it can break down even if not chewed).

Their solution to this problem is to formulate the drug (which has a basic group) with a Eudragit (delayed release type) polymer which has an acidic group "to form a complex". The results report that the taste of the drug could not be detected – presumably because the resulting complex does not break down in the mouth and release the drug, even when chewed.

It must follow, therefore, that the drug is **released later** than it would otherwise have been – which seems to come within the definition of "delayed release". In the conventional immediate release formulation it is liable to be released in the mouth – in this formulation it is not.

Furthermore, since it is not released in the mouth, it must be because it the complex is more resistant to breakdown and/or less soluble, and hence that the drug will be **released more slowly** than in a conventional formulation where the drug is not complexed with the polymer. It therefore also falls within the definition of a controlled release formulation. I would note here that formation of a complex and reducing the solubility of a drug were well known methods of obtaining extended release – see accompanying **Lee & Robinson** (pages 150 and 176-178 from a textbook entitled "Sustained and Controlled Release Drug Delivery Systems", J R Robinson, Ed, Marcel Dekker Inc, NY, 1978; Chapter 3 "Methods to achieve sustained drug delivery").

The definition of "delayed release" is merely that "release ... is modified to occur at a later time" than from a conventional immediate release formulation. But, by definition, this will be true of any "sustained release" formulation: it will go on releasing the drug when release would have stopped in the case of a conventional formulation – ie "at a later time".

So what is meant by release at a later time than that from a conventional immediate release product – can it be minutes, or must it be longer?

Proprietor may argue that the delay in **D24** is likely to be very small – but no quantification of the extent of the delay is given in the claims. If it is intended that the skilled person is to assume that the release of the drug is delayed until after it has passed through the stomach, then the claim should be worded in a manner that makes this clear, so that the public is not put at risk of infringement from formulations that do not have this effect.

A clearer distinction can be seen when the formulation is said to have an "enteric coating", since, by definition, this is specifically designed to delay the onset of release until after the dose has passed through the stomach. Moreover, that is precisely the objective of the release profile for an SSRI, which acts in the GI tract. In other words, "enteric coating" in principle gives a measure of precision to the "delay", and one could then envisage that the formulation thus exposed when the enteric coating is removed has a sustained release

format, allowing it to be thenceforth released at a slower rate than normal.

An "enteric coating" would indeed seem to be different from what is described in **D24**, where the enteric-resistant Eudragit polymer is chemically linked with the drug to form a "complex".

The laconic wording of present claim 1 does not provide the necessary clarity to allow a distinction over **D24**, or more generally over sustained release formulations of paroxetine and other SSRIs.

C. Follow-on comment – inventive step and sufficiency:

The evidence in the opposed patent for reduction of nausea and vomiting is hardly compelling – there are no error factors or statistical significance indicators provided on the figures given, and even the opposed patent acknowledges that there was a "statistically significant centre-by-centre difference" (para 0052).

But even that meagre evidence has only been derived from an **enteric coated** controlled release formulation of paroxetine – ie one that is designed to delay the onset of release until after it has passed through the stomach.

Since the extent of the "delay" encompassed by the claims could be merely a matter of minutes, it is not clear that all formulations falling within claim 1 "solve the problem". It does not seem credible that even the 10% or so difference in the severity of nausea between example (c) (controlled release formulation) and example (d) (controlled release formulation with enteric coating) would also be seen for a delay that allows release of the drug to start in the stomach.

This, therefore, raises a serious issue under Art 56 and/or Art 83.

D. Inventive step – the broader argument:

The arguments I put forward in the notice of opposition still stand, and remain applicable for the reasons indicated below. I will therefore not repeat them here, other than alluding to them in the light of the slightly altered circumstances of the amended claims.

In this submission I will use the document numbering as provided by proprietor.

The OD has emphasised the problem/solution approach, and in our opposition I indicated that any of **D31**, **D32** or **D33** could be taken as the closest prior art. These relate to formulations of the SSRI drug fluvoxamine, where **D31** and **D32** disclose fluvoxamine formulated with an enteric coating, and **D33** provides further information on the side-effect from clinical trials using fluvoxamine.

The problem which I formulated at that time, based on the broader claims then in the case, was:

> ***the provision of a mechanism that alleviates the nausea and vomiting caused by the administration of SSRIs.***

With the claims now narrowed to paroxetine as the SSRI drug, it is not necessarily the case that the problem has to be reformulated, since paroxetine is an SSRI drug, and is administered for that pharmaceutical effect. Moreover, the undesirable side effects noted are those common among SSRI drugs, and not specific to paroxetine.

Thus, the "solution" to the above problem is merely made more precise in that it now becomes that of achieving this end by delayed and controlled release of the drug **and** by the choice of paroxetine as the SSRI.

This is a legitimate approach, since SSRIs are a class of drug aimed at treating a particular type of condition, and such treatment involves choosing a specific drug – ie the physician does not administer a "SSRI", but rather a specific drug that has SSRI properties.

If the "problem" to be overcome with SSRI drugs (the undesirable side-effects) is indeed common to all or most SSRIs, then, unless paroxetine is shown to behave differently in that regard, there is no inventive merit in choosing specifically paroxetine as the "solution", rather than fluvoxamine or any other SSRI drug that exhibits those side effects. In other words, specifying paroxetine in the claims is an arbitrary limitation, and not one that contributes to the solution, or therefore to the inventive step.

Nonetheless, since proprietor has argued from the standpoint of known paroxetine formulations as the closest prior art, I will consider that argument also, based on the "problem" of:

> ***the provision of a mechanism that alleviates the nausea and vomiting caused by the administration of paroxetine as an SSRI.***

D.1 General comment:

Both the patent, and now proprietor in his arguments, admit that the techniques of controlled and delayed release formulation are not in themselves novel or inventive. The invention, therefore, is presented by proprietor as based entirely on the supposed inventive step in the **concept** of adopting both delayed and controlled release for paroxetine – that is all claim 1 specifies. More particularly, proprietor argues that it produces an unexpected effect in reducing the indicated side-effects.

It was obvious that delayed release – at least by enteric coating – will hinder the release of the drug in the stomach, and release it predominantly in the intestine – that is what delayed release oral formulations with enteric coatings do. And it was also obvious that controlled release, in the sense of slower rate of release, will reduce the rate at which the drug is delivered at the site and the rate at which it enters the bloodstream, and hence minimise local irritation and drug serum concentration peaks.

My comments in the notice of opposition in this regard still stand, and have not been properly addressed by proprietor in his response. His argument seems to rest on the presumption that the side effects are caused by a particular mode of action which the skilled person would not believe would be affected by either delayed release or controlled release. But there is nothing in the patent to that effect, and no evidence has been produced that the skilled person before the priority date would have made that assumption.

D.2 Starting from SSRI formulations:

D31 is a review of fluvoxamine, a SSRI drug which, like paroxetine, is CNS-acting via 5-HT receptors in the GI tract, and has side effects of nausea and vomiting. The formulation reported there was enteric-coated, so as to delay its release and thereby

> "minimise gastric adverse effects by reducing the contact of the drug with the stomach mucosa" (page 177, col 1, last para).

It would therefore have been obvious to employ delayed release in the form of an enteric coating in respect of other SSRI drugs, which also have those side effects.

As well as providing a delayed release formulation to alleviate the side effects mediated by contact with the stomach mucosa, **D31** also recognises that

> "Higher plasma concentrations of fluvoxamine may also be associated with an increased incidence of nausea" (page 184, bottom of col 1).

The suggestion for dealing with that is to initiate therapy with comparatively low doses and increasing the dose slowly during the course of the treatment. However, another obvious approach, well-known in the art for controlling plasma levels of a drug, and to reduce side effects generally, is the use of a controlled/sustained release formulation. See, for example, **D1** at page 209, col 1:

> Potential advantages of sustained release drug therapy over conventional drug therapy
>
> 1. Improved control over the maintenance of therapeutic plasma levels of drugs permits...
>
> (c) reduction in the incidence and severity of side effects related to high peak plasma drug concentrations...
>
> 3. There is a reduction in the incidence and severity of localised gastrointestinal side effects produced by 'dose dumping' of irritant drugs from conventional dosage forms...

Proprietor attempts (para 41 of his response) to draw a distinction based on supposed mediation of the side effects by 5-HT receptors in the upper GI tract, rather than serum levels of the drug. No evidence has been provided that the skilled person would have been aware of this and have taken it into account – even if it were presumed to affect his reasoning if he had been aware of it. On the other hand, **D31** does recognize a possible link with drug plasma level, which would tie in with the use of a sustained release formulation to alleviate the situation (**D1**). But even taking the 5-HT receptor mediation argument, this would still tie in with the teaching of sustained release formulations in **D1**, where it is concerned with reducing the local concentration of the drug.

Thus, whether the nausea side effects were thought to be due to high plasma levels of the drug or to localised "dose dumping", an obvious approach to addressing the problem would be to try a sustained release formulation.

In that regard, I would refer to the standard set by the Boards of Appeal in the "obvious to try" scenario, as for example in **T1045/98** at point 17 of the Reasons, and **T333/97** in point 13 para 2 of the Reasons.

There were certainly enough indications of the potential benefits of sustained release in reducing GI side effects for the skilled person to adopt a "try and see" attitude.

It has not been shown that paroxetine is signally different from fluvoxamine in that regard, so as to lead the skilled person to reach a different conclusion; still less that any such knowledge was available to the skilled person before the priority date of the opposed patent. The skilled person must therefore be presumed to think of paroxetine in similar terms to other SSRI drugs as regards amelioration of side-effects that are common to that class of drugs.

D.3 Starting from known paroxetine formulations:

Proprietor argues that the closest prior art should be taken as the immediate release swallow tablets of paroxetine then on the market. However, the closest prior art is not necessarily what is on the market – especially in the pharmaceutical field where it can take years for a drug to reach the market. Thus, **D30** discloses controlled release formulations for use with a wide variety of drugs, including CNS-acting drugs, of which paroxetine is specifically mentioned (page 3 line 33). Furthermore, **D2** clearly teaches that paroxetine can be delivered by slow release (page 2, line 35) – see also **D5** at page 2 lines 26-27.

Any assessment of inventive step, therefore, has to take account of the fact that the concept of administering paroxetine by controlled release was already known, so that whatever effect that might have was either envisaged or would be a "bonus effect" of carrying out that teaching.

Any assessment of inventive step also has to take account of the fact that the concept of administering paroxetine with an enteric coating (ie delayed release) was also known from **D2** (page 2, lines 49-50) and **D5** (page 3 lines 20-22). That is, moreover, consistent with the marketing of the SSRI drug fluvoxamine with an enteric coating, owing to the known mode of action of SSRIs, that they are absorbed in the GI tract, and therefore should ideally by-pass the stomach – whether to avoid loss of drug where it is not needed, or to reduce possible irritation of the stomach mucosa giving rise to side effects (see **D31**, referred to above).

Therefore, the combination of both delayed release and sustained release was making use of measures known to be appropriate and/or potentially useful for SSRIs, and paroxetine in particular. No synergistic effect arises from their combined use; but even it if did, it would be a "bonus effect" of deploying these known measures for their known usefulness.

Other cited documents teach sustained/controlled release of SSRI drugs, as noted in our notice of opposition; in particular **D4/D3a, D28, D29, D30.**

D31 I have already referred to in the preceding section, but the point is that its teachings as regards the SSRI side effects of fluvoxamine would have seen by the skilled person as relevant to other SSRIs that display those side effects, which would include paroxetine. Or to put it another way, the skilled person seeing the side effects of paroxetine, and knowing that they were common among SSRIs, would look to see how they were dealt with – or suggested to be dealt with – in respect of other SSRIs.

D32 also discloses that a marketed formulation of the SSRI fluvoxamine ("Faverin") used an enteric coating – and therefore delayed release.

D33 describes clinical trials of fluvoxamine, and notes its "local irritant properties", and that the side effect is "gastrointestinal", which would be consistent with the advantages indicated in **D1** for a sustained release formulation.

Taking these things together, the skilled person would consider the use of an enteric coating on paroxetine to be very obvious, given that it is an SSRI that is absorbed in the GI tract, and that the SSRI fluvoxamine was commercially produced with an enteric coating.

So from that standpoint, it only remains to ask whether the skilled person would have seen any purpose in also employing a sustained release format – what purpose would it have served, and were there any contraindications known in the art?

The purpose of reducing the side effect of an orally administered drug – any drug – whether induced by local irritation or by drug plasma levels, was well recognised (see eg the textbook **D1**) and would therefore have been common general knowledge. The possibility – indeed likelihood – that one or other of those causes was instrumental in producing the side effects in SSRIs was recognised (see the above-cited documents), and would have made it "worth a try" to use a sustained release formulation with SSRIs – in addition to the delayed release measure to get it past the stomach and into the GI tract – particularly since both delayed release (enteric coating) and sustained release are specifically disclosed in **D2** for use with paroxetine.

There was no indication in the prior art (so far cited) that would have caused the skilled person to believe that it was not worth trying.

D.4 Particular comments on proprietor's response of 23 May 2005:

In relation to our citing **D31, D32** or **D33** as the closest prior art in our original notice of opposition, proprietor merely remarks that they are no longer an appropriate choice for the closest art because the claims are now limited to paroxetine. I have argued above as to why they could still be regarded as the closest prior art, given that the objective is to deliver an SSRI while reducing the known side effects of SSRIs – ie that the "problem" formulated in relation to paroxetine would seem to apply to SSRIs as a class, and therefore that the same problem exists notwithstanding that one arbitrarily specifies a particular SSRI in the claim.

Apart from that, I have argued above that those documents are still relevant even if a paroxetine disclosure is taken as the closest prior art, in view of the commonality among SSRIs – and between paroxetine and fluvoxamine in particular – of the problem being addressed. They are documents that the skilled person, wishing particularly to formulate paroxetine, would take into account.

The rationale put forward by proprietor in para (38) of his submission seems to be a combination of "concerns" that were not self-evidently those of the notional skilled person at the time, or to which the prior art provided remedies from common general knowledge in the field of pharmaceutical formulations.

Thus, proprietor refers to "concentration of paroxetine" in the GI mucosa in the vicinity of the 5-HT receptors as a cause of the side effects; but as **D1** indicates, sustained release formulations are intended to reduce local concentrations of drug. Likewise there is a "concern" that exposure of the receptors lower in the GI tract to "greater concentrations of paroxetine" would cause a problem; but again, **D1** indicates that the reduction of local concentrations of drug to ameliorate adverse side effects is one of the features of sustained release formulations.

In para (39), proprietor refers again to the supposed concern that there would be an increase in the side effect of diarrhoea from using a sustained release formulation. In fact,

the Table in para 0051 shows that there was indeed an increase in the incidence of diarrhoea (both (c) and (d) employ sustained release, and report more diarrhoea than (a) or placebo).

Proprietor's only argument in that regard seems to be that the level of diarrhoea was not "unacceptable". But apart from its being rather a judgment for the patient as to what is acceptable, proprietor's comment at the end of para (38) does not refer to "unacceptable", but merely to the "major concern [that]... by by-passing the upper GI tract, there was a risk that the lower GI tract would be exposed to greater concentrations of paroxetine, thus leading to **increased diarrhoea**". Well, that concern – if it was indeed held by the inventors at the time – seems to have been vindicated by the results shown in para 0051: there was "increased diarrhoea".

So it cannot sensibly be described as a "surprising result" unless it can be shown that the skilled person would have expected a much worse – indeed "unacceptable" – increase in diarrhoea. Since that has not been shown, it should be concluded that the effect of the sustained release formulation on the incidence of diarrhoea is no better than the skilled person would have expected. In other words, that aspect cannot contribute to inventive step.

D.5 Final note on combined delayed + controlled release formulations:

Such combination formulations were in fact well known in the art. **US 5151434** (filed herewith) discloses combined enteric coated controlled release formulations (see eg Examples 3 and 6 and the release data in Fig 1), specifically for addressing the problem of nausea and vomiting side effects. In particular it deals with that specific side effect problem in the context of its being associated with high serum levels of the drug (see col 1 lines 40-50).

It will be recalled that elevated serum levels of the drug was a suspected cause of this side effect in fluvoxamine (see **D31**, referred to above); so although the drug in this US patent is not an SSRI, the skilled person would have applied to fluvoxamine – and likewise to paroxetine – the general principles of drug formulation (see eg **D1**, as referred to above), in the absence of a clear prejudice to the contrary. No such prejudice has been pointed out by proprietor, so this further confirms that what is claimed lacks inventive merit over the prior art.

Footnote – attendance at the oral proceedings:

I shall be accompanied at the oral proceedings by a representative and at least one expert from the opponent company, and possibly a trainee or younger attorney from this firm – so probably four persons in total.

I note from yesterday's submission from the proprietor that he is asking for his client's expert, Dr Sanger, to be able to speak at the oral proceedings "on the nature of the invention and its distinctions from the prior art, particularly on the physiological effects of paroxetine and its GI effects when formulated according to the invention".

I object to that request. Dr Sanger's contribution will of necessity represent new evidence, which should properly have been submitted in writing by now. The description of what Dr Sanger may be asked to contribute seems eminently appropriate for written submission. No explanation has been given as to why it has not been so submitted, and there is no way in

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which the opponent can prepare adequately to deal with technical matters the precise nature of which we will not learn about until the day of the hearing.

Yours faithfully

Ian Armitage
Mewburn Ellis LPP
Authorised Representatives

enc: US 5151434
US 5422123
Lee & Robinson, pages 150, 176-178